(12) UK Patent Application (19) GB (11) 2 118 437 A

(21) Application No **8305029**
(22) Date of filing **23 Feb 1983**
(30) Priority data
(31) **8205937**
(32) **1 Mar 1982**
(33) **United Kingdom (GB)**
(43) Application published
2 Nov 1983
(51) **INT CL^3**
A61K 31/195 31/20
(52) Domestic classification
A5B 170 180 190 20X 20Y
26Y 301 30X 30Y 327 362
36Y 38Y 394 39X J
(56) Documents cited
GB 1159615
(58) Field of search
A5B
(71) Applicants
Efamol Limited,
(Great Britain),
71/74 Mark Lane,
London EC3.
(72) Inventors
David Frederick Horrobin
(74) Agent and/or Address for Service
J. Miller and Co.,
Lincoln House,
296-302 High Holborn,
London WC1V 7JH.

(54) **Composition for treating alcoholism**

(57) A composition of one or more essential fatty acids, for example γ-linolenic acid, in conjunction with glutamine is used to treat alcoholism including mitigating the effects of taking alcohol whether habitually or not and of withdrawal therefrom.

GB 2 118 437 A

SPECIFICATION

Pharmaceutical and dietary composition

Field of the invention

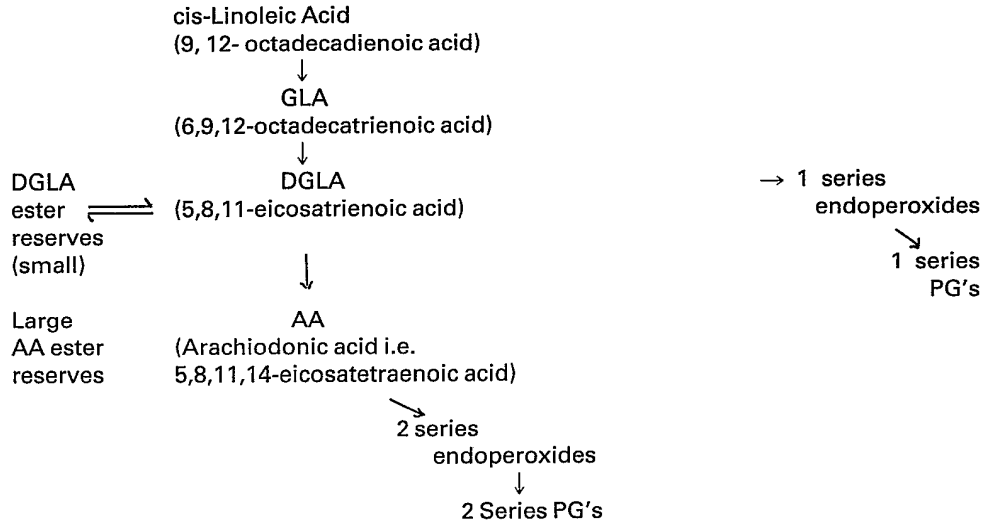
This invention relates to the treatment of alcoholism, or more broadly of any ill effect from taking alcohol and to compositions for use therein.

General background

Considerable interest has been shown in recent years in the use of prostaglandin (PG) precursors in medicine.

For various reasons it is not practical to administer naturally-occurring prostaglandins such as PGE1 and PGE2 to patients for more than a short period. Consequently, considerable attention has focussed on the use of prostaglandin precursors including linoleic acid, γ-linolenic acid (GLA) and dihomo-γ-linolenic acid (DGLA).

Conversion of these materials in the body is believed to be as shown in the following diagram:



The broad outline of this pathway is well known, and it brings out clearly that a major function of essential fatty acids (EFAs) is to act as precursors for prostaglandins, 1-series PGs being formed from dihomo-γ-linolenic acid (DGLA) and 2-series PGs from arachidonic acid (AA). DGLA and AA are present in food in only small quantities, and the major EFA in food is linoleic acid which is first converted to γ-linolenic acid (GLA) and then to DGLA and AA, the latter step being irreversible. The conversion of linoleic acid to GLA is a limiting step, adequate in the young and healthy body but often inadequate in ageing or in many disease states.

DGLA is the key substance, GLA is almost completely and very rapidly converted in the body to DGLA and so for practical purposes the oral administration of DGLA and GLA amounts to the same thing. DGLA can be converted to a storage form, changed to arachidonic acid and then to PGs of the 2-series, or converted to PGs of the 1-series.

A balance between 1-series and 2-series PGs is, the inventor believes, significant in terms of overall control of the conversion pathway given earlier. Such control is not understood in detail but without restriction to the theory it appears first that PGE2 is able to enhance the formation of 1-series PGs, and second that PGE1 is able to block arachidonic acid mobilisation from tissue stores. Thus the conditions for a negative feedback control loop exist; overproduction of PGE2 from AA will activate PGE1 synthesis, the PGE1 will inhibit AA mobilisation, and production of 2-series PGs will drop. Further, TXA2, an unstable product of the 2-series endoperoxides arising in 2-series PG production, also appears to enhance 1-series PG and in particular PGE1 production. Thus again the activity of the 2-series PG synthesis pathway gives rise indirectly to a material that controls that pathway.

Alcohol

The idea that ethyl alcohol may affect PG formation has several times been considered but not with specific reference to 1- or 2-series PGs. The main experimental evidence to date has related to conversion of AA and it has been demonstrated that extremely high levels of ethanol can block the formation of thromboxane B2. The relative effects of alcohol on AA and DGLA conversion have not been considered. The inventor has found that starting at the threshold 20-30 mg%, alcohol has an effect on conversion of DGLA to 1-series PGs, greatly enhancing their production. There is no significant effect on conversion of AA to

2-series compounds until concentrations of above 300 mg% are reached when the effect is an inhibition of thromboxane B2 formation i.e. the opposite action to the effect on the 1-series.

This effect of alcohol can account for a number of its effects, particularly in relation to those on mood. It means that in those who consume large amounts of alcohol there is a considerable danger of depletion of DGLA stores and therefore of a failure of adequate PGE1 production following a period of excess PGE1 formation. This is a particular risk in alcoholics whose dietary intake of many foods is likely to be defective. There is therefore a strong case for ensuring that in those whose alcohol consumption is high, EFA intake should be such that body levels of DGLA are maintained.

Experimentally for example alcohol over the range 30 to 300 mg% causes a marked enhancement of up to 60% in the amount of 14C-DGLA converted to PGE1 in the human platelet system. Up to 100 mg% alcohol has little effect on arachidonate metabolism but at 300 mg% it tends to inhibit conversion of arachidonate to PGs and particularly thromboxanes. The effects on the 1- and 2-series PGs are therefore opposite. The threshold of the effect is at about 20-30 mg% which is the concentration of alcohol in human plasma at which signs of mild intoxication first appear. 300 mg% is a concentration which produces "blind drunkenness".

Alcoholic intoxication will therefore enhance formation of PGE1 and deplete the limited body stores of DGLA. Post-intoxication depression which is such a major factor in the development of chronic alcoholism may well be related to a fall of PGE1 formation due to depletion of DGLA stores. The withdrawal syndrome in chronic alcoholics is often schizophrenia-like and may be caused by extremely severe DGLA depletion. Further, there is evidence that depletion of PGE1 formation is associated with increased production of fibrous tissue, so that the development of liver cirrhosis in some chronic alcoholics may be related to chronic depletion of DGLA. Incidentally the stimulation of PGE1 formation by ethanol explains the reported desirable effects of modest consumption of alcohol (insufficient to deplete DGLA) such as prevention of heart attacks and resistance to viral infections.

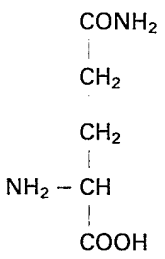
Thus DGLA and materials giving it in the body (the "oil", see later) are of value in at least three ways:

1. In mild to moderate consumers of alcohol, to help prevent depletion of body stores of DGLA, post-intoxication depression and other short and long term features such as elevated cholestrol levels related to essential fatty acid deficiency.
2. In chronic alcoholics undergoing withdrawal, to replenish DGLA stores and maintain PGE1 formation, thus preventing the worst features of withdrawal.
3. In chronic continuing consumers of alcohol, to partially or completely avoid long term adverse effects such as cirrhosis of the liver.

All the above is as discussed generally in the inventor's published European Patent Specification No. A 0 019 423 to which reference may be made for more detail.

Glutamine

Glutamine is a naturally occurring amino acid of formula:



which has the unusual property of being able to pass the blood/brain barrier readily. It is known to be capable in both animals and humans of reducing a craving for alcohol and thus of making reduced intake more likely (R. Williams, The Prevention of Alcoholism through Nutrition, Bantam Books, New York, 1981).

Williams is one of the world's leading nutritionists, yet his book does not mention essential fatty acids. Clearly he does not regard them as significant in relation to alcoholism.

The present inventor has however seen that to combine the approach based on essential fatty acids, as discussed earlier herein, with the use of glutamine, is to achieve most valuable results. Essential fatty acids prevent or reverse some of the adverse effects of alcohol on the body and reduce the severity of the consequences of alcohol withdrawal. Glutamine reduces the appetite for alcohol. Used together they ameliorate the effects of reduction of intake, so that the reduction is not so difficult, and actually reduce the desire to take alcohol, so that a powerfully enhanced effect is obtained.

The invention

The invention thus lies in a composition and method for treating alcoholism (in which is included mitigating the effects of taking alcohol whether habitually or not and of withdrawal therefrom), making use in combination of essential fatty acids, particularly GLA and DGLA, and glutamine. The glutamine is preferably as such but may be in the form of a physiologically acceptable derivative convertible to it, or having the same effect as it, in the body.

Suitable amounts of essential fatty acids are given below. Suitable amounts of glutamine are 10 mg to 30 g/day, preferably 1 to 4 g/day.

The invention may further be used in conjunction with the inventor's previous proposals for selectively enhancing 1-series PG production or, more broadly expressed for influencing the 1-series/2-series PG balance in the body in favour of 1-series PGs. These proposals include use of zinc, β-lactam antibiotics and other materials listed and discussed in published European Patent Specifiction No. A 0 003 407 use of penicillamine, phenformin and levamisole, and colchicine, Vinca alkaloids and other materials listed and discussed in published European Patent Specification No. A 0 004 770; use of vitamin C, ethanol and opiate antagonists listed and discussed in published European Patent Specification No. A 0 019 423; and use of 4-amino and 8-amino quinolines, acridines, quinine and other materials including spironolactone listed and discussed in published European Patent Specification No. A 0 036 856. Referene may be made to these specifications for the full listings, discussion and dosages, which are applicable in the present context also.

The use of Vitamin C is particularly valuable, as it is effective, readily available and safe even in large doses.

Packs

If it is not desired to have compositions comprising the active materials together, as listed above, packs may be prepared comprising the materials presented for separate or part joint and part separate administration in the appropriate relative amounts, and such packs are within the purview of the invention.

Dietary compositions

The invention is chiefly described in terms of pharmaceutical compositions, but it will be understood that the γ-linolenic and other acids, being in the nature of dietary supplements, could be incorporated in a dietary margarine or other foodstuffs; such foodstuffs, possibly containing other active materials and generally referred to in this description as dietary or pharmaceutical compositions, are within the purview of the invention and thus of the term pharmaceutical compositions, packs or the like used in the claims.

Amounts of γ-linolenic and other acids specifically

A preferred daily dosage for all purposes for an adult (weight ca 75 kg) is from 0.05 to 0.1 up to 1, 2, 5 or even 10 g as required of γ-linolenic acid or equivalent weight calculated as γ-linolenic acid or a physiologically functional derivative thereof. Amounts in particular may be 0.1 to 1.0 g daily. Corresponding doses of the Oenothera oil containing 8 to 10% of γ-linolenic acid, are easily calculated. In place of, or in addition to γ-linolenic acid, one may use dihomo-γ-linolenic acid or a physiologically functional derivative thereof, in amounts equivalent in molar terms to γ-linolenic acid and caclulated as such. Other EFA's are likewise related back to γ-linolenic acid in molar terms. The dosage can for example be taken as a single dose or divided into 2, 3 or 4 subdivisions thereof as convenient.

Forms and sources of γ-linolenic and other acids

Convenient physiologically functional derivatives of γ-linolenic acid and dihomo-γ-linolenic acid for use according to the invention for all the purposes described include the C_1-C_4 alkyl (e.g. methyl) esters and the glycerides of the acids.

If desired, pharmaceutical compositions may be produced for use in the invention by associating natural or synthetic γ-linolenic acid (or a physiologically functional derivative thereof) and/or dihomo-γ-linolenic acid (or a physiologically functional derivative thereof), as such, with an acceptable pharmaceutical vehicle. It is at present convenient to incorporate the γ-linolenic acid into compositions in the form of an available oil having a high γ-linolenic acid content, hence references to "oil" herein.

At the presenttime known natural sources of oils having a high γ-linolenic acid content are few (there are no known natural sources of significant amounts of dihomo-γ-linolenic acid). One source of oils currently available is the seed of Evening Primrose species such as *Oenothera biennis L.* and *Oenothera lamarckiana*, the oil extract therefrom containing γ-linolenic acid (about 8%) and linoleic acid (about 72%) in the form of their glycerides together with other glycerides (percentages based on total fatty acids). Other sources of γ-linolenic acid are Borage species such as *Borago officinalis* which, though current yield per acre is low, provide a richer source of γ-linolenic acid than Oenothera oil. Recent studies on fungi which can be cultivated by fermentation promise a fungal oil source.

The seed oil extracts referred to above can be used as such or can for example if desired be fractionated to yield an oily composition containing the triglycerides of γ-linolenic and linoleic as the main fatty acid components, the γ-linoleic acid content being if desired a major proportion. Seed oil extracts appear to have a stabilising effect upon any dihomo-γ-linolenic acid or physiologically functional derivative thereof.

Pharmaceutical presentation

The compositions according to the invention are conveniently in a form suitable for oral, rectal, parenteral or topical administration in a suitable pharmaceutical vehicle, as discussed in detail for example in Williams U.K. Patent Specification No. 1 082 624, to which reference may be made, and in any case very well known generally for any particular kind of preparation. Thus for example tablets, capsules, ingestible liquid or powder preparations, creams and lotions for topical application, or suppositories, can be prepared as

required. Injectable solutions of hydrolysed Oenothera oil may be prepared using albumin to solubilise the free acid.

Advantageously a preservative is incorporated into the preparations. α-Tocopherol in a concentration of about 0.1% by weight has been found suitable for the purpose.

It will be understood that the absolute quantity of active ingredients present in any dosage unit should not exceed that appropriate to the rate and manner of administration to be employed but on the other hand should also desirably be adequate to allow the desired rate of administration to be achieved by a small number of doses. The rate of administration will moreover depend on the precise pharmacological action desired.

The following Examples serve to illustrate pharmaceutical compositions useful in treatment according to the invention.

Examples

Pharmaceutical compositions contain a unit dose of an oil extract from the seeds of *Oenothera biennis L.* and of one of the active materials of the present invention, optionally with methyl dihomo-γ-linolenate and/or any of the other active materials referred to herein directly or by cross reference to other patent applications of the inventor. They may be presented by encapsulation of the natural oil in soft gelatin capsules by known methods.

The oil is extracted from the seeds by one of the conventional methods of extraction such as cold pressure, screw pressure after partially cooking the seed, or solvent extraction.

Fractionation of a typical sample of this oil shows a yield of 97.0% oil in the form of methyl esters, with the relative proportions:

Palmitate	6.15
Stearate	1.6
Oleate	10.15
Linoleate	72.6
γ-linolenate	8.9

As preservative, α-tocopherol is added to the oil in a concentration of 0.1%.

Gelatin capsules containing oil extracts prepared as described above, each have the following contents of active ingredients (0.5 g oil extract = ca 0.045 g γ-linolenic acid), are prepared in conventional fashion.

The following are specific examples of capsules that may be given, two capsules three times a day, in treatment of the conditions listed earlier.

Example 1

Oil extract	0.5 g
Glutamine	0.5 g

Two capsules may be administered thrice daily in the treatment of alcoholism, giving a daily dose of γ-linolenic acid of ca 0.27 g.

Example 2

Similarly to Example 1 capsules containing the following may be administered:

Oil extract	0.5 g
Methyl dihomo-γ-linolenate	10 mg
Glutamine	0.3 g

Example 3

Capsules as in Example 1 or 2 may be administered containing or in conjunction with 0.5 g vitamin C.

CLAIMS

1. A pharmaceutical or dietary composition comprising one or more essential fatty acids in conjunction with glutamine.

2. A composition according to claim 1, wherein the or each essential fatty acid is γ-linolenic acid or dihomo-γ-linolenic acid or a physiologically functional derivative thereof.

3. A composition according to claim 1 or 2 presented for administration to give 0.05 to 10 g γ-linolenic

acid daily or molar equivalent of dihomo-γ-linolenic acid, derivative or other essential fatty acid.

4. A composition according to any preceding claim presented for administration to give 10 mg to 30 g glutamine daily.

5. A composition according to claim 4, wherein said amount is 1 to 4 g daily.

6. A pharmaceutical pack comprising the materials set out in any preceding claim presented separately, or one or more separately and others together, but for joint administration.

7. When for use in the treatment of alcoholism (in which is included mitigating the effects of taking alcohol whether habitually or not and of withdrawal therefrom), the composition of any of claims 1 to 5 or the pack of claim 6.

Printed for Her Majesty's Stationery Office, by Croydon Printing Company Limited, Croydon, Surrey, 1983.
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.